DRAWING AMENDMENTS

Amend Figures 4 and 7.

REMARKS

This amendment is submitted in an earnest effort to bring this application to issue without delay.

Applicants wish to reiterate their claim to the benefit of their Danish priority date of 7 August 2002 pursuant to the International Convention. A certified copy of Danish patent application PA 2002 01189 filed 7 August 2002 has been made of record as part of Applicants' PCT/EP2003/008359 of which the instant application is the US National Phase. The Examiner has already acknowledged Applicants' perfected right of priority.

Applicants have inserted no prohibited new matter into this application.

Applicants have amended the specification to make it clear that SEQ ID NO:1 refers to the polynucleotide sequence in Fig. 4 and not to the polypeptide sequence. Applicants have amended the table on pages 22 and 23 of the specification to indicate SEQ ID NOS: 5 through 12 next to each corresponding polynucleotide sequence.

Applicants are enclosing a new sequence listing in both computer readable form and as a paper copy. The new sequence listing includes SEQ ID NOS: 5 through 12 as indicated above.

Applicants also attach a Statement Under 37 CFR 1.825 signed by the undersigned attorney, licensed to practice before the US Patent and Trademark Office in patent cases, stating that no prohibited "new matter" has been inserted into the application by submitting the substitute pages of the sequence listing and that the computer readable sequence listing and the paper sequence listing contain identical information.

Applicants have amended the drawings in Figures 4 and 7 to include the SEQ ID NOS for the respective polynucleotide sequences.

Applicants have amended claims 1 through 9, 15, 18 through 26, and 31. Antecedent basis for the amendments may be found in the specification on pages 3 through 19 and in Examples 1 and 2. Antecedent basis for the changes in the claims is found especially at the bottom of page 3, page 6, line 14, and in Example 2. Thus claims 1 through 9, 15, 18 through 26 and 31, presently under examination, remain in the application and are again presented for examination.

In addition claims 11 through 14, 16, 17 and 28 through 30, currently withdrawn from further consideration, are believed to be linked to the claims under examination, once these claims are amended to require that the avipoxvirus is grown in avian cells and comprises in its viral genome, a Vaccinia virus host range gene, capable of surprising growth in Avian cells, such as CEFs, to obtain an avian poxvirus with a surprisingly higher titer than that of a corresponding avipoxvirus without the added Vaccinia virus host range gene. Applicants would like to amend those claims withdrawn from further consideration by the Examiner to indicate the common technical feature, linking all claims together, that the avipoxvirus is grown in avian cells to obtain an avian poxvirus with a surprisingly high viral titer so that the withdrawn claims can again be re-linked with the examined claims. See the first paragraph of page 2 of the office action.

The Examiner has rejected claims 1,2,4 through 9, 15, and 26 as anticipated under 35 USC 102 citing TARTAGLIA et al US Patent 6,004,777. Applicants have amended claim 1 to make it clear that the avipoxvirus according to the present invention has been grown in avian cells and has an increased viral titer. Applicants have amended claim 1 to recite the specific Vaccinia virus host range

genes specified on page 5, lines 16 and 17 of the application. Applicants believe that amended claim 1 will patentably distinguish over the FANG et al and TARTAGLIA et al references, even without the proviso. Both FANG et al and TARTAGLIA et al disclose the preparation of a recombinant avipoxvirus vector with host range genes from a Vaccinia virus grown in mammalian cells, especially human cells. The motivation for these projects appears to be increased expression of heterologous DNA included in the avipoxvirus vectors. See for instance the mention in FANG et al (abstract) of HeLa cells (human cervix carcinoma cells) and the mention in US Patent 6,004,777 to TARTAGLIA et al in col. 28 of HeLa cells and human MCR-5 cells (human lung cells) as the cells in which the recombinant avipoxvirus has been grown. There is no disclosure in either TARTAGLIA et al or FANG et al of growing in avian cells an avipoxvirus containing in its genome the specified host range genes from Vaccinia virus and no suggestion in either reference that one would obtain a much higher viral titer of the avipoxvirus grown in avian cells where the avipoxvirus contains the Vaccinia virus host range genes than when the avipoxvirus does not contain the host range gene from Vaccinia virus. Accordingly no rejection of any claim now presented should be maintained under 35

USC 102 as anticipated or under 35 USC 103 as obvious in view of either of these two references.

TARTAGLIA et al in col. 28 discloses that vCP300 exhibited diminished expression in comparison to vCP1452. In col. 24, line 45 ff, vCP300 has been specified as an ALVAC recombinant containing HIVgp120TM,gag/pro, Nef and Pol (i.e. no Vaccinia virus host range gene has been mentioned). Furthermore in col. 28, it is stated that vCP1452 (Vaccinia H7/K31 expression cassette with Vaccinia E3L gene, see col. 24, lines 12 to 16) demonstrated enhanced expression. However, enhanced expression is not the same as an increased viral titer obtained according to the presently claimed invention. Thus the reference is neither a basis for the anticipation or the obviousness of any claim now presented.

The K3L gene disclosed in TARTAGLIA et al and FANG et al is not a classical Vaccinia virus host range gene. Functionally the K3L: gene is an interferon resistance gene. Furthermore the K3L gene, disclosed in both FANG et al and TARTAGLIA et al, is not included in the list of host range genes on page 5 of the present application, and required in claim 1 as now presented. Since

Applicants have included only the specified host range genes on page 5 of the application in amended claim 1, here is a further basis to distinguish over the prior art disclosure of a recombinant avipoxvirus with the K3L gene from Vaccinia virus. Applicants do realize that the host range gene E3L is disclosed in the prior art references TARTAGLIA et al and FANG et al, and is within the scope of present claim 1. However, the reference to the growth of the avian pox virus with the specified Vaccinia host range genes in avian cells with a higher titer than the titer obtained when the avian pox virus is grown in avian cells without the specified Vaccinia virus host range genes is neither disclosed nor suggested in any prior art reference.

Applicants are not sure whether the Examiner believes that the proviso in original claim 1 fails to distinguish the original claims over FANG et al and TARTAGLIA et al or whether the Examiner is actually misinterpreting the proviso and incorrectly believes that what Applicants have excluded from the claims by the proviso, is really what Applicants are including within the claims. See the first substantive paragraph on page 4 of the office action, and the paragraph bridging pp 5 and 6 of the official action. Even more importantly see pages 7 through 11 of the office action,

especially the first paragraph of page 8 and the paragraphs that follow. The Examiner indicates that Applicants are claiming an avipoxvirus containing a Vaccinia virus host range gene used as a vector for an anti-HIV vaccine and that the K3L host range gene is specifically required as at least one of the host range genes when in fact this particular host range gene is excluded from the presently claimed avipoxvirus. Furthermore Applicants are claiming an avipoxvirus viral vector that may be used in preparing an anti-HIV vaccine, but there is no requirement that Applicants use the vector for such a purpose.

Applicants reemphasize that claim 1 as now amended and all of the other claims now in this application are neither anticipated nor rendered obvious by either FANG et al or TARTAGLIA et al since Applicants have now included mention of the higher viral titer of the Avipoxvirus containing the specific host range genes and grown in avian cells in comparison to the titer obtained when the corresponding avipoxvirus is grown on the same avian cells but without the specified Vaccinia virus host range genes. Applicants have data in Example 2 that show that when an avipoxvirus (e.g. canarypox virus) is grown in avian cells (e.g. CEF cells) and the Vaccinia virus host range C7L gene, flanked by

homologous sequences to the canarypox virus, is incorporated into the canarypox virus through homologous recombination, the resulting canarypox virus is obtained in a surprisingly high titer, in fact better than one order of magnitude than the viral titer obtained without the incorporation of the C7L host range gene from Vaccinia virus. Furthermore when the same canarypox virus and the same Vaccinia virus host range genes flanked by the same canarypox virus sequences are added to mammalian cells, rather than CEFs or other avian cells, there is no corresponding improvement versus the control in the rate of growth of the recombinant canarypox virus at all. Other cells tested included BHK-21, Vero, 143B, HaCaT, HeLa, MRC-5, and RK-13. Applicants believe that this evidence is surprising and should be the basis for obtaining allowance of the claims now presented.

The Examiner has rejected claim 18 as anticipated under 35 USC 102 in view of US Patent 5,494,807 to PAOLETTI et al. The Examiner states that Applicants claim an avian cell infected with an avipoxvirus and a Vaccinia virus, yet he argues that the disclosure in PAOLETTI et al of the vaccination of mice with a Vaccinia virus vaccine and an avipoxvirus vaccine anticipates the claim. Applicants find no disclosure or suggestion in PAOLETTI et

al of avian cells infected with an avipoxvirus and a Vaccinia virus with the specified host range genes. In any event Applicants have now limited claim 18 to require that the cell is an isolated avian cell, and have more sharply defined the host range gene as in the case of claim 1 above, and have included the requirement that the avipoxvirus grown in avian cells with the Vaccinia virus host range gene is obtained in a surprisingly higher viral titer than the titer obtained when the same avipoxvirus does not contain the Vaccinia virus host range gene and so the claim is neither anticipated by nor rendered obvious by PAOLETTI et al.

The Examiner has rejected claims 1 through 9, 15, 19, 26 and 31 as obvious citing the combination of FANG et al, TARTAGLIA et al and PERKUS et al. The Examiner believes that FANG et al anticipates the presently claimed invention, but for the fact that Applicants insert Vaccinia virus host range gene C7L into an avian poxvirus. However, the Examiner believes that PERKUS discloses the importance of including the Vaccinia virus host range genes K1L and C7L in human cell cultures to permit growth of the Vaccinia virus. Without these two host range genes, PERKUS et al discloses that it is not possible to grow Vaccinia virus in non-avian (e.g. human) cells. The Examiner concludes that it would be obvious from PERKUS

et al to incorporate the C7L Vaccinia virus host range gene in an avipoxvirus with the expectation of obtaining a poxvirus that can replicate in human cells. It appears that the Examiner is relying on the TARTAGLIA et al disclosure of incorporating the K3L and E3L Vaccinia virus host range genes into a Canarypox virus as discussed hereinabove.

From the way that the Examiner has framed the argument for obviousness by combining FANG et al, TARTAGLIA et al and PERKUS et al, Applicants further believe that the Examiner is misreading the proviso in claim 1 and that he believes that the matter that Applicants have excluded by proviso, is actually the subject of the claim. The fact that PERKUS et al discloses that deleting the Vaccinia virus host range gene C7L from that virus, prevents replication of that virus in humans, has absolutely nothing to do with the present invention. Applicants disclose a recombinant avian poxvirus, and disclose its replication in avian cells, not in human cells. Applicants have deliberately picked an avian poxvirus because these poxviruses do not readily replicate in human cells, making them ideally suited as viral vectors for human administration. See the bottom of page 2 of the present application. It would be desirable for Applicants to use an avian

poxviral vector that can infect humans to express a heterologous gene from the viral genome, while at the same time avoiding risk to the human patient of replication of the poxvirus itself. This it is not seen how the disclosure in PERKUS et al is suggestive of the invention especially as Applicants now claim it since Applicants are not seeking to prepare a recombinant avipoxvirus that can replicate in human cells.

The Examiner's argument on page 7 of the office action that claims 1 and 7 through 9 are not supported by an enabling disclosure under 35 USC 112, first paragraph further underscores Applicants' belief that the Examiner has misinterpreted the proviso in claim 1 as originally presented. The Examiner understands that Applicants are preparing a recombinant canarypox virus with the C7L Vaccinia virus host range gene, but seems to believe that the very specific HIV genes disclosed in FANG et al and TARTAGLIA et al in combination with the Vaccinia virus host range genes E3L and K3L are part of the present invention as well. The Examiner's arguments set forth on pages 7 through 9 of the office action that the Applicants' claimed invention is not sufficiently supported by the disclosure of the invention in the specification is not well

founded because the Examiner has misinterpreted the scope of the claims since he has misread the proviso.

The Examiner's argument on pages 9 through 11 of the office action that claims 18, 20 and 21 are not supported by an enabling disclosure are incorrect for the same reasons that the arguments above for claims 1 and 7 through 9 are not correct.

Applicants now have the following direct comments regarding the FANG et al, TARTAGLIA et al and PERKUS et al references and the claims as now presented.

None of the cited prior art references deals with the problem of increasing titer of avipoxviruses.

PERKUS et al is directed to host-range restriction of vaccinia viruses. The reference does not give any hint that it is possible to use vaccinia virus host range genes or homologues thereof to increase the titer of avipoxviruses. Furthermore, it has to be stated that contrary to the presently claimed invention PERKUS et al concerns the replication of fowlpoxviruses in mammalian cells. The present invention is directed to avipoxviruses comprising Vaccinia host range genes, which have been shown to

increase the titer in avian cells which allow the reproductive replication of the avipoxviruses. Summarizing, the cited reference is completely distinct from the present invention.

PERKUS et al reports the identification of the C7L host range gene and that K1L, C7L or CP77kDa is sufficient to overcome restriction of vaccinia virus replication on pig kidney cells and that either the K1L or the CP77kDa gene, but not the C7L gene, allows vaccinia virus replication on rabbit kidney cells (page 276, right col., lines 6-8 and lines 15-21). However again, PERKUS et al is directed to replication of vaccinia viruses (not an avipoxvirus) in human cells, which are normally non-permissive. This has nothing to do with the present invention providing an avipoxvirus grown in avian cells comprising a vaccinia host range gene.

FANG et al and TARTAGLIA et al are directed to vectors comprising E3L and/or K3L genes and gene expression. However, neither of these references suggests an avipoxvirus grown in avian cells comprising in the viral genome a vaccinia virus host range gene or a homologue of said host range gene, wherein the avipoxvirus containing the Vaccinia virus host range gene is obtained in a surprisingly higher titer than the titer obtained for

the corresponding avipoxvirus without the Vaccinia virus host range gene. Specifically, neither FANG et al nor TARTAGLIA et al discloses or suggests an avipoxvirus comprising a host range gene as required in claim 1 which increases the titer of avipoxviruses in avian cells.

FANG et al discloses that the addition of vaccinia E3L and K3L genes to ALVAC-HIV vectors represents a novel attempt to increase antigen expression through the addition of modulatory genes to an attenuated poxviral vaccine vector (page 279, right col., lines 2-6). In particular, FANG et al is directed to enhancing antigen expression in human cells (see the abstract).

The teaching of FANG et al does not suggest the subject-matter of the claims. An attempt to increase antigen expression in a canarypox vector in human cells is not related to increase of avipoxvirus titer in cells permitting replication of avipoxviruses. An interaction of complex mechanisms (including viral and immunological components) is needed for the replication of viruses. As described in the specification, avipoxviruses are host restricted to avian species and cells, and do not replicate in human cells (see page 2, lines 29-page 3, line 2). Surprisingly the

Applicants found that when a Vaccinia host range gene is inserted into a avipoxviruses its titer increases in avian cells; this has nothing to do with possible enhanced antigen production in human cells as described in FANG et al. Even though the antigen production would increase in human cells, it cannot be predicted that the viral titer would increase in human cells because of host-restriction and other regulatory mechanisms. In fact, it would not be desirable that a viral vector would have an increased replication in human cells. Therefore, gene expression and the viral titer do not have a direct dependency and an increase of antigen production does not suggest an increased titer. Thus, nowhere was it suggested that the avipoxviruses of the invention would increase the titer or permissive cells and it is indeed surprising that an avipoxvirus comprising a vaccinia host-range gene has an increased titer in avian cells.

Furthermore, FANG et al, in particular, recites that "*the addition of immunomodulatory genes to attenuated poxviruses represents a novel strategy for enhancing antigen production*" (last line of abstract) and "*we note that the addition of immunomodulatory genes to attenuated poxvirus vaccine vectors is*

not unique to this study. Attenuated poxviruses expressing human tumour antigens combined with B7.1 and interleukin-2 or with granulocyte/macrophage-colony stimulating factor as immunoadjuvants have demonstrated promising results in mice" (page 280, left col., lines 9-16). Thus, this provides further evidence that FANG et al indicates E3L and K3L as immunomodulatory genes, and does not suggest in any way that vaccinia host-range genes would increase the titer of avipoxviruses in avian cells. It was indeed surprising that when a vaccinia host range gene was added to avipoxvirus vector the titer in CEF cells was increased ten fold.

TARTAGLIA et al describes recombinant ALVAC vectors comprising E3L/K3L ORFs in ALVAC under the control of early vaccinia promoters (see page 12, lines 9-13). In particular, TARTAGLIA et al is directed to utilizing vaccinia encoded functions (e.g. E3L, K3L) to increase the levels and persistence of gene expression (e.g. foreign gene expression) in vectors (page 3, lines 6-11). Thus, TARTAGLIA et al deals with gene expression and not viral titres of avipoxviruses and therefore, does not suggest that the avipoxviruses comprising a host-range gene would have an increased titre in permissive cells.

None of PERKUS et al, FANG et al or TARTAGLIA et al suggests an avipoxvirus comprising a vaccinia host range gene as required in claim 1, 18, 19 or the dependent claims. Therefore, the subject-matter of all the claims now presented is based on an inventive step, and so no rejection of any claim now presented should be maintained on the grounds of either anticipation or obviousness.

On page 11 of the office action the Examiner has indicated that he believes that claims 22 through 25 would be allowable if written in independent form with all intervening limitations of preceding claims on which these claims directly or indirectly depend. Applicants appreciate the Examiner's indication of allowability. These claims are directed to a particular feature of the present invention where the host range gene from the Vaccinia virus and the canarypox virus are both included within the avian cell, but where the host range gene is not integrated into the Avipoxvirus. Applicants still seek, however, protection as well for the avipoxvirus, grown in avian cells and obtained in a surprisingly high titer, in which is incorporated a Vaccinia host range gene such as C7L.

On page 11 the Examiner has requested that Applicants before claim 1 replace "CLAIMS" with - WHAT IS CLAIMED IS -. Applicants have made this amendment.

Once the Examiner has had a chance to consider the Applicants' amendments to the claims and arguments in support of the patentability of the presently claimed invention over the cited prior art, Applicants would like to schedule a telephone interview with the Examiner.

Applicants believe that all claims now presented are in condition for allowance and a response to that effect is earnestly solicited.

Respectfully submitted,
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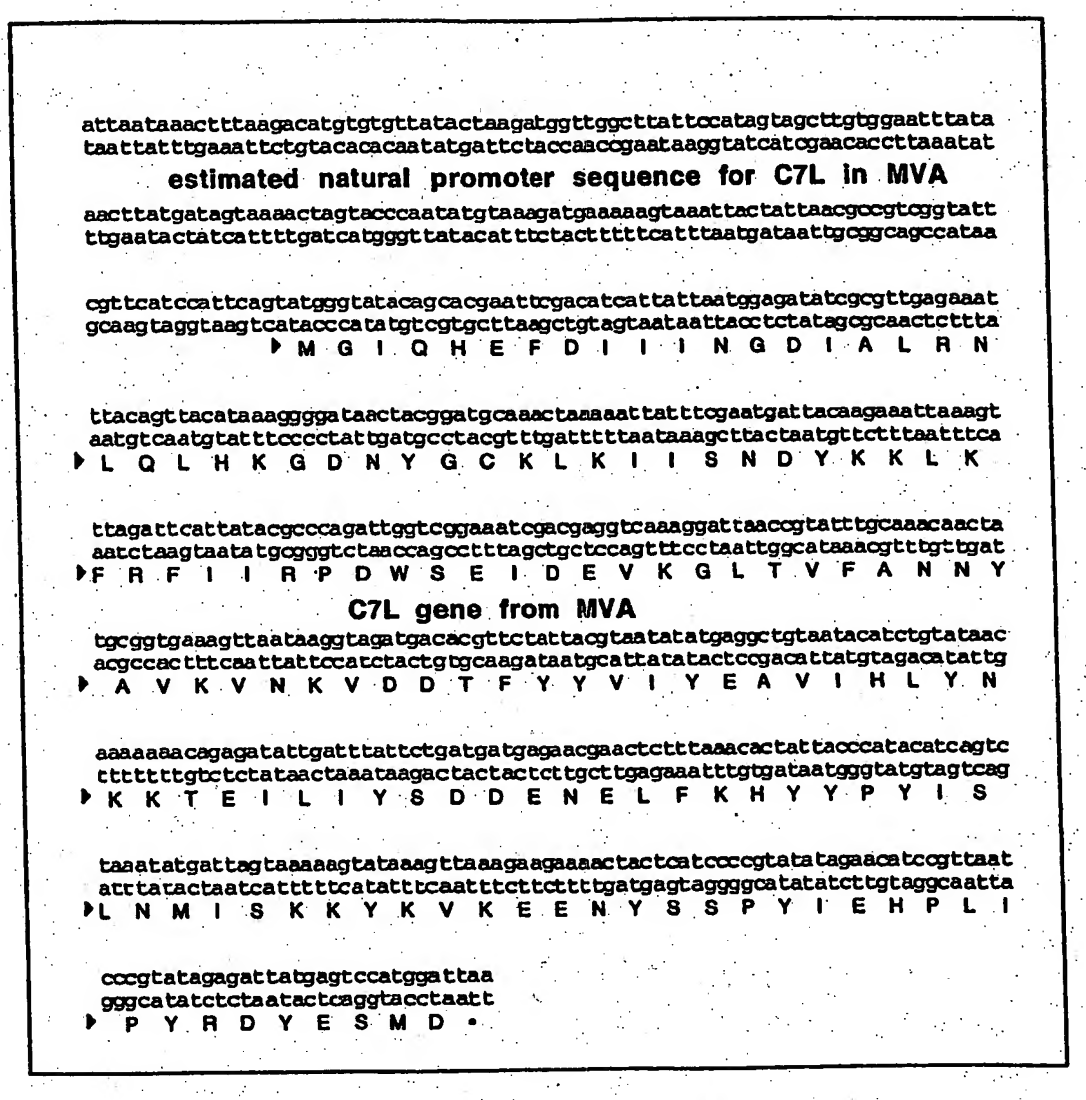
Enclosure:
PTO notice to comply with sequence listing
computer-readable sequence listing
paper copy sequence listing
sequence listing declaration
amended Figures 4 and 7

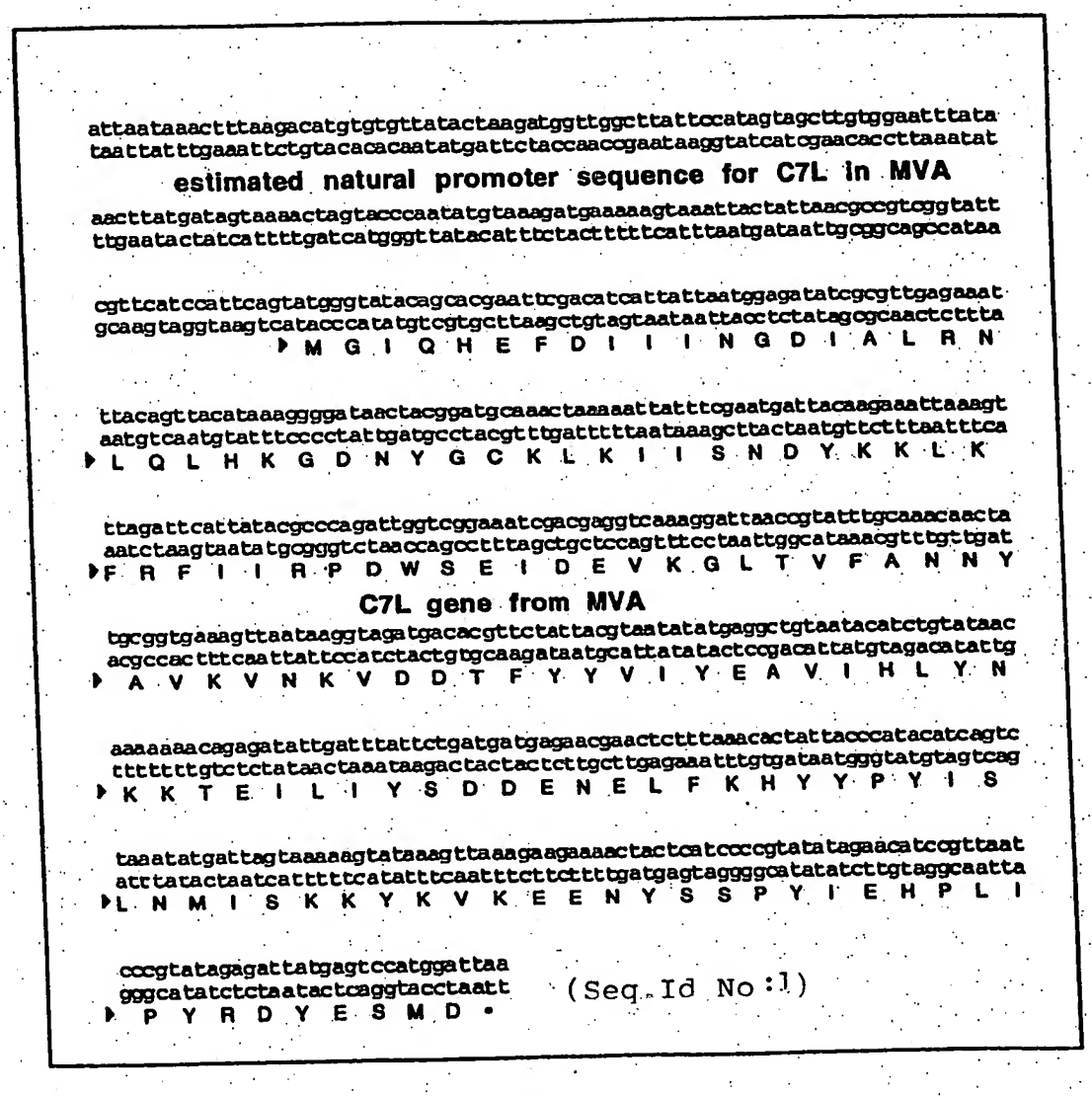
(Original Version)

Figure 4:



Ser No 10/524043 23117

Figure 4:



(Seq. Id No:1)